Editorial

SARS-CoV-2 infection and the human immune system: A continuing journey of discovery

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The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has precipitated the worst global pandemic in a century, causing millions of infections and deaths. SARS-CoV-2 research continues to be a dominant topic of submissions to the ***Proceedings*** as illustrated by the cluster of four SARS-CoV-2 articles in this issue.[1–14] In leading off this cluster, Le *et al.*[15] help us understand the unique pathogenic interactions between SARS-CoV-2 and the human immune system. This article reviews the current understanding of the innate and adaptive immune responses to SARS-CoV-2 infection, including their relationship to current therapeutic and diagnostic strategies. Expanding on this theme, other articles within the SARS-CoV-2 cluster are directed to investigating how defects in the human immune system impact the response to SARS-CoV-2 infection, a subject of which little is currently known.

In particular, patients with hereditary angioedema (HAE) have been postulated to be at increased risk for coronavirus disease 2019 (COVID-19) infection due to inherent dysregulation of the plasma kallikrein-kinin system. However, because only limited data have been available to explore this hypothesis, in this issue, Veronez *et al.*[16] direct a major investigative effort to explore this relationship. They report the results of an online questionnaire–based study designed to gather information with regard to complications, morbidity, and mortality among patients with HAE and with self-reported COVID-19 infection. The investigators found that the subjects with HAE C1 inhibitor (C1-INH) who were not taking HAE medications had a significantly higher rate of reported COVID-19 infection.[16] They also found that the use of subcutaneous C1-INH and icatibant was associated with a significantly reduced rate of reported COVID-19 infection.[16] These findings implicate potential roles for the complement cascade and tissue kallikrein-kinin pathways in the pathogenesis of COVID-19 in patients with HAE C1-INH and offer new potential modes of therapy for this potentially devastating dual combination of disease entities.

Of particular interest to the allergist, is research with regard to allergic reactions seen in patients receiving messenger RNA (mRNA) COVID-19 vaccines and strategies to assure the safety of a second-dose administration. In this issue, Patel *et al.*[17] reported on their assessment of the safety and utility of a two-step graded-dose protocol for the second dose of mRNA vaccines in patients with a history of low suspicion of anaphylaxis to their first dose. This was a retrospective evaluation of 77 patients who presented with a reaction to either the Pfizer-BioNTech or the Moderna vaccine in which most patients (69.7%) had symptom onset within 4 hours.[17] Recommendations included either proceeding with routine administration of the second dose (70.1%), using a two-step graded dose (19.5%), or deferral (10.4%).[17] Twelve of 15 patients completed the second dose with a graded-dose protocol; of these, five reported similar symptoms as experienced with their first dose.[17] The authors found that most patients with presumed allergic reactions to their first dose of COVID-19 mRNA vaccine were able to safely receive the second dose. They concluded that, for vaccine reactors with a low suspicion of anaphylaxis, the two-step graded-dose protocol could be an effective strategy for second-dose vaccination, especially for those who may otherwise defer the second dose.

Another COVID-19 topic of interest to the allergist is related to the question of how allergic diseases affect the severity of COVID-19 infection. In this issue, Vezir *et al.*[18] reported on their investigation of the relationship between allergic diseases and COVID-19 severity in 75 pediatric patients who were evaluated and classified according to clinical severity 1 to 3 months after their COVID-19 infection resolved. The authors report no difference in severity between patients with and those without asthma. The median total immunoglobulin E level was significantly higher in the asymptomatic/mild group.[18] The authors conclude that aeroallergen sensitization and allergic rhinitis in children may be associated with a milder course in COVID-19 infections.

A second major cluster of articles in this issue focus on the topic of asthma. Olgaç *et al.*[19] sought to characterize paucigranulocytic asthma phenotype in 116 adult patients with asthma and who were non-

smokers. By using the methodology of induced sputum cell count analysis, four distinct phenotypes could be identified: eosinophilic (24%), mixed (6.9%), neutrophilic (7.8%), and paucigranulocytic (62.9%).[19] Sputum macrophages were found to be higher in paucigranulocytic asthma when compared with the other three phenotypes.[19] Both a lower uncontrolled asthma ratio and a lower forced expiratory volume in the first second of expiration reversibility pattern were also found to be prominent characteristics of the macrophage predominant phenotype.[19] Pan *et al.*[20] conducted a meta-analysis to assess the use of YKL-40 levels as a diagnostic marker of asthma. Their analysis suggested that increased serum levels of YKL-40 in patients with asthma could be used as an emerging indicator for distinguishing individuals with asthma from healthy individuals.

Also included in this issue are two review articles on the efficacy and safety of the anti-inflammatory prodrug corticosteroid, ciclesonide, by Blaiss *et al.*[21,22] The first article is directed to the efficacy of ciclesonide for the treatment of asthma in children and the other on the safety of ciclesonide in children with asthma. Based on their review of efficacy data from eight phase III, randomized, double-blind, controlled trials in children with asthma, the authors conclude that, in children with asthma, once-daily ciclesonide is comparable with other inhaled corticosteroids in that it significantly improved large and small airway function, asthma symptoms, and asthma control and reduced rescue medication use compared with placebo. Based on their review of the safety data from 13 studies, the authors conclude that ciclesonide is associated with low rates of oropharyngeal adverse events with no indication of clinically relevant systemic effects in children with asthma. The authors suggest that the favorable safety profile of ciclesonide and its demonstrated improvement in asthma control make it an ideal inhaled corticosteroid for the treatment of asthma in children.

A report by Wallace[23] transitions the subject matter from asthma treatment to a mechanistic approach of treating the underlying type 2 inflammation associated with chronic sinusitis with nasal polyps (CRSwNP). The author provides a comprehensive review, comparing and contrasting the therapeutic recommendations presented by the European Position Paper on Rhinosinusitis and Nasal Polyps 2020[24] and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021.[25] The therapeutic options that she discusses include intranasal and oral corticosteroids, corticosteroid-eluting implants, saline solution rinses, oral aspirin desensitization, antifungal agents, oral and topical antibiotics, antileukotrienes, oral antihistamines and decongestants, and biologics (dupilumab, omalizumab, mepolizumab, and reslizumab) as well as surgical intervention. Wallace[23] concludes that we still lack an evidence-based CRSwNP treatment algorithm for when to recommend surgery and/or initiate or discontinue biologics to maximize quality of life and cost-effectiveness.

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion, based on the inability to identify a causal relationship between a trigger and an anaphylactic event despite a detailed patient history and careful diagnostic assessment. Burrows and Ellis[26] review the prevalence of IA, comorbid atopic conditions, differential diagnosis, acute and long-term management of IA, and the potential role of biologics as steroid-sparing agents. The authors conclude that the lack of diagnostic criteria, finite treatment options, and intricacies of the differential diagnosis contribute to the challenge of managing patients with IA.[26] Because of the importance of this information to patients who suffer from this condition, it was chosen as the basis for this issue's ***"For the Patient"*** section entitled "Idiopathic anaphylaxis." This segment, found in the final pages of the print version of this issue and also available online, consists of a one-page article synopsis written in a readily comprehensible fashion to help patients better understand the content of the full article.

Immunoglobulin replacement therapy (IGRT) is the foundation of treatment for the majority of patients with primary immunodeficiency disorders. In this issue, Wasserman[27] reviews the clinical history and laboratory evaluation that define patients for whom IGRT is necessary and appropriate. He provides very practical advice on how to assess candidates for IGRT and how to approach the reevaluation of IGRT recipients to determine the need for continued treatment and/or optimization of IGRT.

Past assessment of care delivered to patients with α-1-antitrypsin deficiency (AATD) has demonstrated an unmet need for improvement in care. Based on this needs assessment and information gap, Ptasinski *et al.*[28] aimed to assess the requirement for continuous quality assessment with regard to the provision of optimal care for a population of patients with AATD in a large health-care system. The authors conclude that care of the patient with AATD can be improved no matter which subspecialty cares for the patient and further demonstrated the need for ongoing quality-assurance programs.[28]

Drug provocation tests (DPT) without skin tests are increasingly recommended in the evaluation of children with low-risk, β-lactam (BL) allergies. However, the challenge is to determine the appropriate candidates for this procedure. Therefore, Demirhan *et al.*[29] aimed to create a clinical predictive model that could help identify appropriate children at low risk who could safely undergo direct DPT. To do so, they analyzed the clinical data of 204 children who underwent a full diagnostic algorithm for suspected BL allergy and used these data to construct mathematical predictive models for confirmed BL allergies. These models showed a sensitivity

of 77.8% and a negative predictive value of 94.3%.[29] A prospective new sample was used to validate the final models. The authors conclude that risk assessment in BL allergies should depend on population-specific predictive models and that this may help to provide an accurate determination of the children at low risk who may safely proceed to direct DPT.[29]

In summary, the collection of articles found within the pages of this issue provides further insight into the intersecting crossroads of inflammation and disease that manifest as allergic, immunologic, and respiratory disorders that afflict patients whom the allergist/immunologist serves. In particular, they exemplify how the complexities of COVID-19, HAE, allergic rhinitis, asthma, CRSwNP, IA, primary immunodeficiency, AATD, and drug allergy continue to challenge the allergist/immunologist. In keeping with the overall mission of the ***Proceedings***, which is to distribute timely information with regard to advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients, it is our hope that the articles found within this issue will help foster enhanced patient management and outcomes. On behalf of the Editorial Board, we hope that you are able to make practical use of the diversity of literature offered in this issue of the Proceedings.

Joseph A. Bellanti, M.D. and
Russell A. Settipane, M.D.

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